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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
09605.0016-00000

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

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Typed or printed name _____

Application Number	§ 371 Date
10/555,286	October 17, 2006

First Named Inventor
Juan M. JIMENEZ MAYORGA

Art Unit	Examiner
1626	Sun Jae Y. LOEWE

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

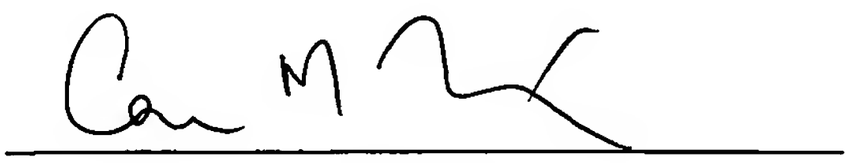
I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.

☐ attorney or agent of record.
Registration number _____.

■ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 48,638


Signature

Carlos M. Téllez
Typed or printed name

202-408-4123
Telephone number

May 15, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

■ *Total of 1 form is submitted.

I. Status of the Claims and Priority Document

Claims 1-15 and 20-25 are pending in this application. Claims 11-15 and 22-25 have been withdrawn by the Office as being directed to non-elected subject matter. The claims under examination, claims 1-10, 20, and 21, have been rejected at least twice. In response to the rejection in the Final Office Action dated January 16, 2009, ("Final Office Action"), Applicants respectfully request a pre-appeal brief review of the outstanding rejection.

Additionally, further to the Office's indication that a certified copy of the priority document could not be found in the PTO's file, Applicants filed a certified copy of the priority application on May 14, 2009. Applicants respectfully request acknowledgement that a claim for foreign priority has been made.

II. Rejection under 35 U.S.C. § 103(a)

Claims 1-10, 20, and 21 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO 2002/014272 in view of Patani and LaVoie, Bioisosterism: A rationale approach in drug design, *Chem. Rev.* 96:3147-3176 ("*Patani*"). Final Office Action at 2; *see also* Office Action of July 22, 2008, at 5.

According to the Office, WO 2002/014272 teaches "compound 401470-74-4" as a VLA-4 antagonist. Office Action of July 22, 2008, at 6 and caplus abstract. The Office states that *Patani* teaches that sulfone (-SO_2-) is a bioisostere of the carbonyl group. *Id.* The Office argues that *Patani* teaches "that sulfone moieties have been increasingly used as bioisosteres." *Id.* In response to Applicants' arguments filed October 22, 2008, the Office argues that "[o]ne or ordinary skill would have chosen the cited compound based on the prior art disclosure - eg. see pg. 22." Final Office Action at 3. The Office further asserts that "[t]he modification would have been within the level of ordinary skill

(ie. see disclosure of Patani et al.)." *Id.* Finally, the Office states that "one of ordinary skill would have a reasonable expectation of success in obtaining an additional compound for the cited activity." *Id.* Applicants respectfully disagree and traverse.

a. To establish obviousness of a new chemical compound, the Office must identify not only a lead compound, but also a reason to modify such compound in a particular manner

In a recent decision addressing the standard for obviousness of chemical compounds, the Federal Circuit stated that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound." *Eisai Co., Ltd. v. Dr. Reddy's Laboratories*, No. 2007-1397, 1398, slip op. at 8 (Fed. Cir. 2008). Moreover, once a suitable starting point has been established, there must also be "a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.'" *Takeda Chem. Ind., Ltd. v. Alphapharm Pty., Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007) (citations omitted). Thus, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new compound." *Id.* (underlining added).

These recent decisions require that the Office: a) identify a compound that would have been considered by one of ordinary skill in the art as suitable for further modification, and b) explain the reasons why such skilled artisan would have made the specific modifications proposed by the Office to arrive at the claimed invention.

Moreover, even under the "obvious to try" rationale advanced by the Office in the Office Action of July 22, 2008, it remains necessary that one of ordinary skill in the art

would have had "a reasonable expectation of success" in making the modifications proposed by the Office. M.P.E.P. § 2143.E. As will be shown below, the Office has not complied with any of the above requisites and Applicants will present below *three* *independent* reasons for withdrawal of this rejection.

b. **Reason 1**—The Office has not shown that compound 401470-74-4 would have been considered a suitable compound for further modification by one of ordinary skill in the art

The Office suggests that "[o]ne of ordinary skill would have chosen the cited compound based on the prior art disclosure - eg. see pg. 22." However, page 22 of WO 2002/014272 provides Table 1, which simply lists compound 401470-74-4 as working example no. 4. Applicants note that Table 6 on p. 30 compares IC_{50} data obtained from various compounds, including compound 401470-74-4. A low IC_{50} value is desired because it indicates that a lower concentration of the test compound is needed to inhibit the VLA-4 integrin activity by half. Applicants note there are eleven compounds, out of twenty-four, with lower IC_{50} values than compound 401470-74-4. No information is provided to support selecting 401470-74-4 (the twelfth most active compound) as a lead. Accordingly, there is no reason why one of ordinary skill in the art would have selected compound 401470-74-4 from WO 2002/014272 as a lead compound.

For at least this reason, the Office has not made a *prima facie* case of obviousness and Applicants respectfully request that this rejection be withdrawn.

c. **Reason 2**—According to *Patani*, the teachings therein regarding bioiosteres apply to lead compounds, and the Office has not shown that compound 401470-74-4 is a lead compound

The Office argues that *Patani* teaches "that sulfone moieties have been increasingly used as bioisosteres" of the carbonyl group. Office Action of July 22, 2008,

at 6. However, *Patani* only suggests "modification of lead compounds." *Patani* at page 3147, col. 2 (underlining added). That is, the teachings of *Patani* are applicable once one of ordinary skill in the art has identified a suitable compound as a lead compound for modification in order to obtain "safer and more clinically effective agents." *Id.*

Therefore, one of ordinary skill in the art would not have applied the alleged modification taught by *Patani* to compound 401470-74-4 because, as explained above, this compound has not been identified in WO 2002/014272 as a lead compound.

d. **Reason 3**—The disclosure in *Patani* shows that replacement of a carbonyl group with a sulfone group, as suggested by the Examiner, results in compounds with ***less*** activity

The Office has failed to provide "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention," as required. *See Takeda*, 83 U.S.P.Q.2d at 1174. The Office asserts that "[t]he modification would have been within the level of ordinary skill (ie. see disclosure of Patani et al.)." Final Office Action at 3. Applicants understand the Office to be arguing that, because *Patani* teaches that the sulfone moiety is a bioisostere of the carbonyl group, such knowledge would have motivated one of ordinary skill in the art to make the substitution of the carbonyl group for sulfone in compound 401470-74-4. However, the Office has ignored *Patani's* results showing that in every instance when the carbonyl group was substituted with sulfone, the activity of the resulting compound decreased. For example, the replacement of the carbonyl in an antagonist of an LTB_4 receptor with sulfone reduced the inhibitory activity of the compound from 85% to 79%. *Patani* at Table 39, p. 3167 (compare the activity of compound 82 a, having the carbonyl group and displaying 85% inhibition, with compound 82f, having the sulfone

group and showing 79% inhibition). Also, the replacement of the carbonyl group in an euglycemic agent by a sulfone group reduced the activity of the compound from 100% to 69%. *Id.* at Table 41, p. 3168[1] (compare the activity of compound 85a, having the carbonyl group and 100% glucose normalization, with compound 85b, having the sulfone group and showing 60% glucose normalization). Therefore, the teachings in *Patani* would not have led one of ordinary skill in the art to replace a carbonyl group by a sulfone group in compound 401470-74-4 because of the expectation that such modification would lead to compounds with less biological activity than that of compound 401470-74-4.

Additionally, the Office states that "one of skill would have a reasonable expectation of success in obtaining an additional compound for the cited activity." Final Office Action at 3. However, the Office does not appreciate that the modification actually lead to compounds with less biological activity than that of the parent compound, as discussed above, and thus might also lead to a complete loss of activity. Accordingly, there would not have been a reasonable expectation of success.

In summary, it remains unclear: a) why one of ordinary skill in the art would have selected compound 401470-74-4 from those disclosed in WO 2002/014272 for further modification and b) why one of ordinary skill in the art would have modified compound 401470-74-4 as suggested by the Office. Accordingly, the Office has not made a *prima facie* case of obviousness and Applicants request that this rejection be withdrawn.

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[1] The results in *Patani's* Table 40 do not involve a replacement of a carbonyl group by a sulfone group and are not relevant to the present analysis.